REMARKS

Upon entry of this amendment, Claims 1-63 and 65 constitute the pending claims in the present application. Among them, Claims 1-27, 32, 43-45, 47, 56-62, and 65 are directed to non-elected inventions and are withdrawn from further consideration. Applicants will cancel these claims upon indication of allowable subject matter. Claims 28-31, 33-42, 46, 48-55, and 63 are directed to the elected invention. Applicants have canceled Claims 64 and 66 without prejudice. Applicants reserve the right to prosecute claims of identical or similar scope in future continuation or divisional applications.

Applicants note that the inventorship of the instant application has been corrected pursuant to 37 C.F.R. § 1.48(a). Applicants further note that the three previously filed IDS's have been considered by the Examiner.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Drawings

The Office Action objects to the drawings filed on March 4, 2002 for failing to separately describe the individual panels of certain figures in the "Brief Description of the Figures" section of the specification, thus violating 37 C.F.R. 1.84(p)(5).

Applicants have amended the "Brief Description of the Figures" section to insert the respective descriptions to obviate this objection. Applicants submit that no new matter is introduced by these amendments. Reconsideration and withdrawal of the objection are respectfully requested.

Claim objections

The Office Action objects to Claims 64 and 66 for allegedly being improper multiple dependent claims. Applicants have canceled these claims without prejudice to obviate the objection. Applicants reserve the right to prosecute claims of identical or similar scope in future continuation / divisional applications. Reconsideration and withdrawal of the objection are respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 38-42, 48, and 49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Office Action indicates that Claim 38 recites "wherein R1 binds to or inhibits a kinase," and Applicants have elected methotrexate as R1, which Claim 38 reads on. Thus, the Office Action asserts that this is inconsistent with the specification, which teaches that "...R2 is intended to be a kinase inhibitor (*e.g.*, page 76, last paragraph; Example 2), such as a kinase inhibitor selected from Table 2."

Applicants submit that the recitation of R1 as being a kinase inhibitor results from a typographical error, which Applicants have corrected by amending Claim 38. Applicants submit that the amendment does not introduce new matter (see for example, page 76, last paragraph; Example 2; and original Claim 37), and does not narrow the scope of the claim. Reconsideration and withdrawal of the rejection are respectfully requested.

The Office Action also rejects Claims 42, 48, and 49 as allegedly being indefinite, because they recite "derivative" and/or "minor structure modifications," the metes and bounds of which terms are allegedly unclear.

Applicants have amended Claims 42 and 48 to clarify the subject matter claimed. Support can be found, for example, in the first paragraph of page 81.

Applicants submit that "derivative" (of an original compound) as defined by the specification (and as used in the claims) includes those molecules that share with the original compound the effective moiety for binding, but may have other structural modifications. By way of example, the specification illustrates that methotrexate (Mtx) only uses its 2,4-diaminopteridine double-ring structure to bind DHFR. Therefore, compound 2,4-diaminopteridine, which has the same 2,4-diaminopteridine double-ring binding moiety, is a "derivative" of Mtx within the scope of the invention.

Thus, "derivative" as used in the amended Claims 42 and 48 not only provides a concrete definition identical to the support in the specification, but also contains both structural and functional limitations in the definition: structurally, the derivative must share the effective

binding moiety with the original compound, although other structural modifications may be present; functionally, however, the derivative must still bind the same binding partner (*e.g.*, ligand binding domain of the screening system). Thus, a skilled artisan can clearly determine whether a compound structurally similar to a named compound qualifies as a "derivative thereof," simply based on a structural and functional comparison with the original compound. The metes and bounds of the amended claims are clear. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph are respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph - enablement

Claims 38-42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The thrust of this rejection rests on the notion that Claim 38 recites R1 as being a kinase inhibitor, and the elected species methotrexate does not appear to be a kinase inhibitor.

As discussed above, such recitation of R1 in Claim 38 is due to a typographical error, which Applicants have corrected by amending Claim 38. The amended Claim 38 correctly recites the user-specified R2 as kinase inhibitor, and the specification provides numerous examples of such R2 in, for example, Table 2. Thus, the amended Claim 38 is fully enabled. Reconsideration and withdrawal of the enablement rejection are respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph – written description

Claims 28-31, 33-42, 46, 48-55, and 63 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the invention(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Office Action asserts that the claims recite "derivatives with minor structural modifications." With respect to the elected species R1 – methotrexate, the instant specification describes only the methotrexate structure, but not "alteration of the structure, which retains the binding capacity with respect to its ligand." Applicants respectfully disagree.

First of all, the instant specification does disclose, in the first paragraph of page 81, that methotrexate (Mtx) only uses its 2,4-diaminopteridine double-ring structure to bind DHFR. Furthermore, the specification teaches that compound 2,4-diaminopteridine has the same 2,4-diaminopteridine double-ring binding moiety as Mtx, and is thus a "derivative" of Mtx within the scope of the invention. Thus at least with respect to Mtx, a skilled artisan would immediately envision a genus of compounds sharing the same 2,4-diaminopteridine double-ring binding moiety as Mtx, and could reasonably conclude that Applicants were in possession of the genus.

Secondly, as discussed above, Applicants have amended Claims 42 and 48 to clarify the subject matter claimed. Applicants submit that amended Claims 42 and 48 (and their dependent claims) provides derivatives of the recited original compounds, wherein the derivatives are related to the original compounds by both structure and function. Thus, describing each of the recited original compounds (which are all well-known with defined structures) also provides a representative description for the entire genus of compounds encompassing the respective original compounds. In each case, a skilled artisan could immediately envision the entire genus based on the known structure of the named original compounds, and would thus reasonably conclude that Applicants are in possession of the entire genus. Reconsideration and withdrawal of the written description rejection are respectfully requested.

Claim rejections under 35 U.S.C. § 102

The Office Action states that claims 38, 42, 52, 53, and 63 are rejected under 35 U.S.C. § 102(a) as being anticipated by Lin et al. Applicants respectfully disagree.

Regarding Claim 38, Lin does not teach a hybrid ligand R1-Y-R2, wherein R2 binds or inhibits a kinase. The Office Action rejection is based on the erroneous assumption that methotrexate is a kinase inhibitor R2. Even if dexamethasone (Dex) in Lin is interpreted as "R2", it binds glucocorticoid receptor (GR) – a nuclear transcription factor. Thus, Lin cannot anticipate Claim 38 and its dependent Claims 42, 52, and 53.

Regarding Claim 63, Lin does not disclose any business method, nor does it teach any linker "of the general structure $(CH_2\text{-}X\text{-}CH_2)_n$." Thus, Lin cannot anticipate Claim 63 and its dependent claims.

The Office Action further states that Claims 28, 30, 31, 33, 34, 46, 52, 53, and 63 are rejected under 35 U.S.C. § 102(b) as being anticipated by Keenan (*Bioog. Med. Chem.* **6**: 1309-35, 1998) as evidenced by Amara (*Proc. Natl. Acad. Sci. U.S.A.* **94**: 10618-2, 1997) and Bierer (*Proc. Natl. Acad. Sci. U.S.A.* **87**: 9231-35, 1990). Applicants respectfully disagree.

As to Claims 46, 52, 53, and 63, Keenan does not teach that "R1 is different from R2." In fact, "R1" and "R2" in Keenan have to be identical in order for the ligand taught in Keenan to be functional, because all the ligands in Keenan are built to dimerize proteins (see title of Keenan and Table 1). Thus, Keenan cannot anticipate Claims 46, 52, 53, and 63.

As to Claim 28 (and its dependent Claims 30, 31, 33, 34, 52, and 53), Applicants submit that Keenan also fails to teach a screening method to identify a polypeptide that binds to a user-specified ligand, as is claimed in Claim 28. In Keenan, a number of ligands with *varying* linkers and/or *varying* binding monomers were tested for their relative abilities to dimerize known binding partners for the monomers, and the resulting biological effects in several assay systems (such as inducing FAS-mediated apoptosis, transcription activation, *etc.*). Keenan never teaches or suggests that the two monomers can be different, nor does it teach or suggest any screening assay in which a library of candidate binding proteins are to be expressed in cells, so that those candidate binding proteins that actually bind one of the two monomers on the ligand (R2) can be identified. In other words, there is no candidate ligand-binding domain P2 in the Keenan assay systems, since both ligand-binding domains in Keenan are both *known* and *invariable* – in Keenan, one can vary either the linker or both monomers; a single monomer cannot be changed while the other remains the same if the conjugate is to be effective for its intended purpose.

In fact, the Examiner agrees (on page 17, first paragraph of the Office Action) that Keenan neither teaches that R1 differs from R2 in the hybrid ligands, nor teaches the screening of a library of nucleic acid sequences (encoding candidate P2). Therefore, Keenan cannot anticipate Claims 28, 30, 31, 33, 34, 46, 52, 53, and 63.

Claims 54 and 55 are allegedly anticipated by Lin in view of Mehta (WO 00/07018), or anticipated by Keenan as evidenced by Amara in view of Mehta (see pages 25-27 of the Office Action). However, since a 35 U.S.C. § 102 rejection over multiple references can only stand if the extra references are cited to: (A) prove the primary reference contains an "enabled disclosure;" (B) explain the meaning of a term used in the primary reference; or (C) show that a

characteristic not disclosed in the reference is inherent (see MPEP 2131.01), Applicants submit that none of these exceptions to the single reference rejection apply. In fact, the Office Action uses the term "it would have been obvious" in explaining the rejections. Thus, Applicants will treat these rejections as being based on 35 U.S.C. § 103(a) and address them below.

In summary, neither Lin nor Keenan teaches or suggests all the elements of the claimed invention. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully rejected.

Claim rejections under 35 U.S.C. § 103(a)

Claims 29 and 36 are rejected under 35 U.S.C. § 103(a) as unpatentable over Keenan in view of Licitra (*Proc. Natl. Acad. Sci. U.S.A.* **93**: 12817-21, 1996), as evidenced by Amara. This is based on the ground that Keenan failed to disclose that R1 differs from R2 in the hybrid ligands, or the screening of a library of nucleic acid sequences (encoding candidate P2), or the use of LacZ reporter genes, while Licitra allegedly teaches such steps.

Specifically, the Office Action asserts that a skilled artisan would be motivated to combine Keenan with Licitra, in order to "receive the expected benefit of being able to identify proteins capable of binding FK506 as taught by Licitra...to use the assay to manipulate the structure of the ligand, as taught by Keenan...to use the LacZ reporter gene to be able to easily visualize positive interactions by testing for blue color formation in the presence of X-gal as taught by Licitra..."

Applicants submit that a skilled artisan would have no motivation to combine Keenan and Licitra, such that the polyethylene linkers (*e.g.*, **1q – 1r**) disclosed in Keenan are used in a hybrid ligand in Licitra, because Keenan teaches away from this specific combination.

In Keenan, a variety of linkers were screened to see if any of them would out-perform the hybrid ligand **1d**, which is the reference compound with an apoptosis IC_{50} of 6 nM, and transcription assay EC_{50} of 15 nM (transient transfection assay) or 20 nM (stable transfection assay). See Table 1 on page 1311. Specifically, compounds **1i** to **1s** were synthesized, each sharing the same FKBP12-binding monomer as that of **1d**, but differing in their respective linker sequences (see Table 1, pages 1311 – 1312; right column, page 1313, to left column, page 1314). Based on these assays, Keenan concludes that the three polyether linkers tested in ligands **1p –**

1r, described as "[a] more radically altered set of compounds" (page 1313, right column, towards the middle of the last paragraph), are "poor" in terms of their ability to induce apoptosis. For example, the reference linker in **1d** has an IC_{50} of about 6 nM. In contrast, the best of **1p – 1r** has an IC_{50} of about 140 nM, about 25 times worse than **1d**.

The same linkers (**1p – 1r**) are also considerably worse than **1d** in both the transient and the stable transfection assays, with EC_{50} between 5-20 times worse than that of **1d** (see Table 1 on page 1312). Over all, among the 11 linkers similarly tested, all but one (**1o**) are better than the polyether linkers in both the apoptosis assay and the transient transfection assay (see Table 1).

Note linker AP1427 (**1k**) is not a polyethylene linker of the claimed invention, because it contains other non-polyethylene moieties (*e.g.*, it does not fit the general formula $(CH_2\text{-}X\text{-}CH_2)_n$ as required by the claims).

Thus, for the sake of argument, even if a skilled artisan would consider both Keenan and Licitra when designing his R1-Y-R2 type hybrid ligand, he would have had no motivation to use any of the worst linkers tested – the polyethylene linkers **1p – 1r** in Licitra's hybrid ligand, which uses a linker essentially identical to that of **1d** (compare the linker in Figure 1, panel **4** of Licitra with the bisamide **1d** linker in Table 1 of Keenan). There is simply no reason, and certainly no teaching or suggestion in Keenan or Licitra, that one should consider replacing a seemingly superior linker **1d** with a far inferior polyethylene linker.

A skilled artisan would also have had no reasonable expectation of success in arriving at the claimed invention, because in view of the data in Table 1 of Keenan, the skilled artisan would probably have eliminated all the tested linkers **1i – 1s** from consideration, since none of these are any better than **1d** (with the possible exception of **1m**). This is almost certainly true with respect to the worst candidates tested – the polyethylene linkers.

The Office Action also rejected Claims 29, 35, 36, 41, and 48-50 as allegedly being obvious over Keenan in view of Licitra and Lin as evidenced by Amara. The same claims are also rejected as allegedly being obvious over Keenan in view of Licitra, Lin, Sota and Karlsson as evidenced by Amara.

However, these rejections rely on the same argument Applicants refuted above, on top of the erroneous assumption that R1 (*e.g.*, methotrexate) is a kinase inhibitor.

In view of Applicants' amendment to Claim 38, the rejection to Claim 41 (a dependent claim of Claim 38) additionally suffers from the defect that the combined teaching fails to teach all the limitations of the claimed invention.

The Office Action also rejects Claims 54 and 55 as being obvious over Lin in view of Mehta, or over Keenan as evidenced by Amara in view of Mehta (see above). These rejections are also based on the erroneous assumption that R1 (*e.g.*, methotrexate) is a kinase inhibitor. Thus, the same infirmity regarding the combined teaching persists.

Therefore, all the requirements for establishing a *prima facie* case of obviousness are not met. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**, under Order No. **DFMP-P01-018**.

Respectfully Submitted,

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Yu Lu, Ph.D.
Reg. No. 50,306

Customer No: 28120
Docketing Specialist
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050